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10/516,430	06/17/2005	Ralph M. Bohmer	311706	2820

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,430	BOHMER, RALPH M.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,32-34 and 47* is/are pending in the application.

4a) Of the above claim(s) *16-30,32-34 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-30,32-34 and 47* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/05; 2/15/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-15, filed November 23, 2007, is acknowledged and has been entered. Claims 16-30, 32-34, and 47 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Currently, claims 1-30, 32-34, and 47 are pending. Claims 1-15 are under examination.

2. Applicant traverses the restriction requirement on the grounds that all the claims recite a common technical feature which is detecting maternal antibodies bound to a fetal cell. Accordingly, Groups I and II should be rejoined.

In response, the inventions listed as Groups I and II are distinct methods that do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is simply an assay method for determining or identifying that fetal cells having paternally-inherited fetal antigens are present in maternal blood sample by binding them to maternally produced antibodies specific thereto; whereas Group II is a method of enriching fetal cells from maternal blood sample by isolating a fraction of mononuclear cells present in the blood sample, contacting the mononuclear cells with maternally produced antibodies specific for paternally-inherited fetal antigens present in fetal cells, and then recovering the cell complexes so as to obtain an enriched population of fetal cells present in maternal blood sample. Specifically, Group II is a method which requires isolation, positive selection, and enrichment method steps which are not specifically required to perform the method of Group I. Accordingly, literature search for each separate method is

distinct since the structural requirements of each invention are different. While searches would be expected to overlap, there is no reason to expect the searches to be coextensive. Therefore, the restriction requirement of record is being maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is ambiguous because it is unclear how "maternal antibody bound to a fetal cell" because it is unclear how a maternal antibody would have binding specificity to a fetal cell, i.e. fetal cell antigen.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 5, 7-9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Warwick et al. (Detection strategy for maternal antibodies against paternal HPA-1 antigen, The Lancet 344: page 64 (July 2, 1994)).

Warwick et al. teach a method of identifying fetal cells (platelets) present in sample (amniotic fluid) to determine fetal cell susceptibility to maternal antibodies. In practice, the fetal cells in the sample are exposed to maternal antibodies, whereupon maternal antibodies that bound to the fetal cells which form fetal cell-maternal antibody complexes, are detected and identified. The maternal antibodies comprise maternally produced antibodies specific for paternal HPA-1 antigens, which are paternally-inherited fetal antigens. Blood samples from each parent of the fetus are also obtained for phenotyping for the presence of HPA-1 antigens. Binding is detected by exposing the maternal antibody-fetal cell complex with a detectably labeled agent that binds the maternal antibody-fetal cell complex or HPA-1 present in the cell; hence forming maternal antibody-fetal cell-agent complex or maternal antibody-HPA-1-agent complex. Binding can be detected of demonstrated using solid phase assays or platelet immunofluorescence technique (see entire document on page 64, column 2).

5. Claims 5, 7-9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Bussel et al. (Antenatal Treatment of Neonatal Alloimmune Thrombocytopenia, The New England Journal of Medicine 319: 1374-1378 (November 24, 1988)).

Bussel et al. teach that neonatal and fetal alloimmune thrombocytopenia results from the formation of a maternal antibody to paternal antigen, usually PLAI, on fetal cells (platelets) (see Abstract). In practice, the fetal cells from (amniotic fluid sample or cord blood sample) are exposed to maternal antibodies (IgG, IgA, and IgM), whereupon maternal antibodies that bound to the fetal cells which form fetal cell-maternal antibody complexes, are detected and identified. The maternal antibodies comprise maternally produced antibodies specific for paternal PLA1 antigens, which are paternally-inherited fetal antigens. Binding is detected by exposing the maternal antibody-fetal cell complex in the fetal sample and

maternal sample with a detectably labeled agent that binds the PLAI that is present in fetal platelet cells; hence forming maternal antibody-fetal cell-agent complex or maternal antibody-PLA1-agent complex. Binding can be detected of demonstrated using antigen capture assay (i.e. ELISA) or platelet indirect immunofluorescence technique (see page 1375, column 1, first, second, and third full paragraphs).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-5, 7-9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simons (US Patent 5,447,842) in view of Warwick et al. (The Lancet 344: page 64 (July 2, 1994)) or Bussel et al. (The New England Journal of Medicine 319: 1374-1378 (November 24, 1988)).

Simons teaches a method for selectively recovering fetal cells from maternal blood sample. The blood sample is obtained from a pregnant woman whereupon maternal cells and fetal cells are separated based on differential reactivities of the cells to antibodies specific for polymorphic cell surface antigens,

particularly HLA antigens. Fetal cells are separated based on their reaction with at most one of the antibodies (see Abstract and column 3, lines 34-41). Differential antibody reactivities between fetal cells and maternal cells can be performed using solid-phase affixed fluorescent-labeled antibodies specific for fetal antigen present in the fetal cells, whereupon fetal cells that bound to the antibodies are detected and separated by fluorescence activated cell sorting (FACS). The label can also be a paramagnetic particle (magnetic bead) whereupon fetal cells that bound to the antibodies are detected and separated by magnet activated cell sorting (MACS) (see column 3, lines 49-62 and column 4, lines 52-62). According to Simons, prior art (Herzenberg et al. and Iverson et al.) has also reported that fetal cells are present in maternal blood as early as 15 weeks gestation, and that fetal cells can be separated from maternal blood by binding the cells to fluorescent-labeled antibodies specific for paternal HLA antigen present in fetal cells and then using fluorescence activated cell sorting (FACS) to separate the fetal cells. Such demonstration that fetal cells enter the maternal blood circulation and can be isolated by FACS enrichment procedures has practical significance in enabling karyotyping without the need for [invasive] amniocentesis (see column 1, lines 32-42 and column 2, lines 1-14).

Simons differs from the instant invention in failing to teach that the antibodies that bound to fetal cells which are specific for paternally-inherited fetal antigens (present in the fetal cells) are maternal antibodies.

Warwick et al. or Bussel et al. have been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Warwick or Bussel of maternal antibodies that are specific for and bind to paternally-inherited fetal antigens, for application with the method of identifying and selecting/separating fetal cells from maternal sample as taught by Simons because Simons specifically recognized and showed

the advantage of cell surface antigen specificity of antibodies in separating specific rare cells from a sample, and Warwick or Bussel suggested that maternal antibodies can be used to bind specific rare fetal cells, specifically those that express paternally-inherited antigen, and Simons specifically taught that such demonstration that fetal cells enter the maternal blood circulation for identification and enrichment procedures, including those bound by maternal antibodies as taught by Warwick or Bussel, has practical significance in enabling karyotyping without the need for [invasive] amniocentesis.

7. Claims 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Simons (US Patent 5,447,842) in view of Warwick et al. (The Lancet 344: page 64 (July 2, 1994)) or Bussel et al. (The New England Journal of Medicine 319: 1374-1378 (November 24, 1988)) as applied to claims 1-5, 7-9 and 11-15 above, and further in view of Tsang et al. (Optimum dissociating condition for immunoaffinity and preferential isolation of antibodies with high specific activity, Journal of Immunological Methods 138: 291-299 (1991)).

Simons, Warwick et al. or Bussel et al. have been discussed supra. Simons, Warwick et al. or Bussel et al. differ from the instant invention in failing to teach that maternal antibodies can be dissociated from a complex with soluble HLA antigen.

Tsang et al. teach dissociating bound antibodies from its antigen matrix by eluting them using various dissociation reagents (see Abstract and page 294, column 2 bridging to page 295, column 1 and Figure 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Tsang in dissociating antibodies from their antigen matrix into the method of Simons as modified by Warwick or Bussel which identifies and separates rare cells based on their antigen

expression and reactivity because Tsang specifically taught that by dissociating these antibodies and maintaining their function and binding activity, they can be used for application with immunological methods whereupon rare cells having selected antigen specificity can be detected or enriched for isolation purposes such as for application in karyotyping without the need for [invasive] amniocentesis.

8. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Simons (US Patent 5,447,842) in view of Warwick et al. (The Lancet 344: page 64 (July 2, 1994)) or Bussel et al. (The New England Journal of Medicine 319: 1374-1378 (November 24, 1988)) as applied to claims 1-5, 7-9 and 11-15 above, and further in view of Sisson et al. (An Improved Method for immobilizing IgG antibodies on protein A-agarose, Journal of Immunological Methods 127: 215-220 (1990)).

Simons, Warwick et al. or Bussel et al. have been discussed supra. Simons, Warwick et al. or Bussel et al. differ from the instant invention in failing to teach that the polypeptide which binds to immunoglobulin is protein A, protein G, or protein L.

Sisson et al. teach that protein A binds the Fc portion of immunoglobulin molecules, specifically, IgG molecules, leaving antigen specific sites free; hence improving the antigen binding capacity of IgG. Sisson et al. further teach that the complementary interaction between protein A and the constant Fc region of IgG allows predictable immunoglobulin immobilization to its intended substrate.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Sisson in protein A binding specificity to Fc portion of IgG into the method of Simons as modified by Warwick or Bussel which identifies and separates rare cells based on their antigen expression and reactivity because Sisson specifically recognized and showed the advantage of using protein A in binding immunoglobulins, so as to allow predictable immunoglobulin immobilization to its

intended partner, such as in this case, rare fetal cells expressing paternally inherited antigens, intended for detection, enrichment, or isolation purposes such as for application in karyotyping without the need for [invasive] amniocentesis.

9. No claims are allowed.

Remarks

10. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Holzgreve et al. (Prenatal Diagnosis using Fetal Cells and Free Fetal DNA in Maternal Blood, Metabolic and Genetic Screening 28 (2): 353-362 (June 2001)) teach isolating fetal cells from maternal blood sample by exposing fetal cells to monoclonal antibodies specific for fetal erythroblasts whereupon the antibodies bind to CD71 or GPA cell surface antigens present on the erythroblasts (see Abstract and page 354).

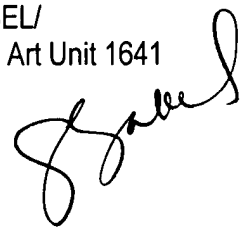
Wegmann et al. (Allogeneic Placenta is a Paternal Strain Antigen Immunoabsorbent, The Journal of Immunology 122 (1): 270-274 (1979)) show that antibody specific for antigens coded by murine HLA complex (H-2) disappears rapidly from bloodstream of females pregnant by males bearing the appropriate antigen, and that the placenta differentially absorbs the antibody when the fetus bears the target antigen; thus, serving as a paternal antigen immunoabsorbent for neutralizing maternal antibody directed against the fetus (see Abstract and page 270, column 2).

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641



February 15, 2007